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ORAL MUCOSITIS: PREVENTION AND MANAGEMENT- A SHORT COMMUNICATION

KOTYA NAIK MALOTH, VELPULA NAGALAXMI, NAGA JYOTHI MEKA & LALITHA CH

Oral Medicine and Radiology, Sri Sai College of Dental Surgery, Andhra Pradesh, India

ABSTRACT

Oral mucositis is a common sequel of radiotherapy, chemotherapy, and radio-chemotherapy in patients with cancer or patients requiring hemopoietic stem cell transplants. Mucositis has a direct and significant impact on the duration of disease remission and cure rates, serving as a subjective indicator of the co-morbidity. Mucositis also affects survival because of the risk of infection and has a significant impact on quality of life and cost of care. This paper aims at a brief review of oral mucositis with emphasis on its prevention and management strategies.

KEYWORDS: Cancer, Chemotherapy, Radiotherapy, Oral Mucositis, Management

INTRODUCTION

Oral mucositis refers to erythematous and ulcerative lesions of the oral mucosa caused by cancer therapy. It is most common complication seen in the cancer patients being treated with chemotherapy or with radiation therapy or both to fields involving the oral cavity. The incidence of oral mucositis was especially high in patients having primary tumours in the oral cavity, oropharynx or nasopharynx and patients who are undergoing chemotherapy, radiotherapy (total dose over 5000 cGy) treatment modalities and those treated with altered fractionation radiation schedules (hyper fractionation)[1]. Clinical Significance of the oral mucositis can be explained by its symptoms being very painful subsequently affecting nutritional intake, mouth care, and quality of life. Moderate to severe oral mucositis has been correlated with systemic infection and transplant related mortality.

PATHOGENESIS OF MUCOSITIS[2]

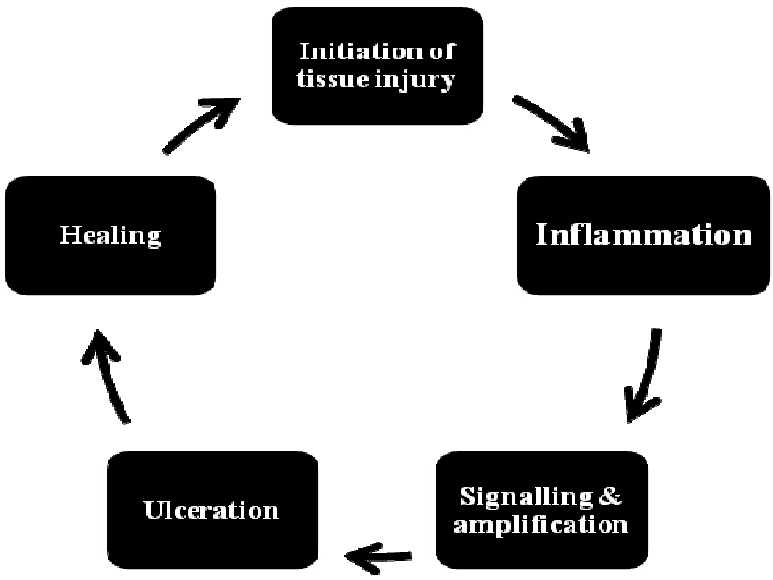

Table 1

Initiation	Cell exposure to chemo- and radiotherapy causes DNA damage and generation reactive oxygen species (ROS), which are able to injure cells, tissues and blood vessels
Signaling	ROS cause further DNA damage and stimulate expression of transcription factors that lead to tissue injury and apoptosis
Amplification	Release of pro-inflammatory cytokines result in further tissue damage, which amplifies the signalling cascade
Ulceration	Painful ulcers form that provide an entry point for bacteria, viruses and fungi. Bacterial cell wall components can further induce inflammation and necrosis.
Healing	A signal from submucosal tissue allows renewed cellular proliferation and differentiation restoring the lining of the oral cavity

CLINICAL COURSE OF ORAL MUCOSITIS

Oral mucositis initially presents as erythema of the oral mucosa, which then often progresses to erosion and ulceration. The ulcerations are typically covered by a white fibrinous pseudo membrane. In chemotherapy-induced and radiation-induced oral mucositis, lesions are usually limited to non-keratinized surfaces. Ulcers typically arise within 2 weeks after initiation of chemotherapy and in radiotherapy more than 5000 cGy to the oral mucosa will develop severe ulcerative oral mucositis. Viral infections such as recrudescent herpes simplex virus (HSV) and fungal infections such as Candidiasis can sometimes be superimposed on oral mucositis. Although HSV infections do not cause oral mucositis, they can complicate its diagnosis and management[3].

MEASUREMENT OF ORAL MUCOSITIS

Oral symptoms function scales and validated measures of tissue damage currently represent the best means of assessing the oral mucositis.

The World Health Organization (WHO) scale and the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 includes separate subjective, objective and functional measures of scale for mucositis[4].

Table 2

	WHO Scale	NCI-CTC Clinical	NCI-CTC Functional
Grade 1	Oral soreness, erythema	Erythema	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function
Grade 2	Ulcers but able to eat solids	Patchy ulcerations or pseudomembranes	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL(Activities of daily living)
Grade 3	Oral ulcers and able to take liquids only	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL
Grade 4	Oral alimentation impossible	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Symptoms associated with life-threatening consequences
Grade 5	Not available	Death	Death

The Oral Mucositis Assessment Scale (OMAS) is an objective scale, suitable for research purposes, that measures erythema and ulceration at nine different sites in the oral cavity[5].

Table 3

Oral Mucositis Assessment Scale (OMAS)		
Location	**Ulceration**	**Erythema**
Lip (upper & lower)	0, 1, 2, or 3	0, 1, or 2
Buccal mucosa(right & left)	0, 1, 2, or 3	0, 1, or 2
Tongue ventrolateral (right & left)	0, 1, 2, or 3	0, 1, or 2
Floor of mouth	0, 1, 2, or 3	0, 1, or 2
Palate (hard & soft)	0, 1, 2, or 3	0, 1, or 2

0 = none; 1 = <1 cm^2; 2 = 1–3 cm^2; 3 = >3 cm^2.
0 = none; 1 = not severe; 2 = severe.

INVESTIGATIONS

The investigations performed are Cell morphology and viability of exfoliated buccal cells and Trypan blue dye exclusion test.

CLINICAL MANAGEMENT OF ORAL MUCOSITIS

Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) has developed clinical practice guidelines for the management of mucositis[6].

- Pain Control
- Nutritional Support
- Oral Decontamination
- Palliation of Dry Mouth
- Management of Oral Bleeding
- Therapeutic Interventions for Oral Mucositis

Pain Control: The primary symptom of oral mucositis is pain. This pain significantly affects nutritional intake, mouth care, and quality of life. The management of pain includes avoiding oral irritants (smoking, alcohol, or rough or spicy foods) which aggravates the pain, Saline mouth rinses (bland oral rinses), ice chips, topical mouth rinses containing an anaesthetic such as 2% viscous lidocaine and applying topical analgesics to combat pain and dysphagia when used before meals. The Anaesthetics agents such as lidocaine, dyclonine, or diphenhydramine, coating agents, such as milk of magnesia, liquid Amphogel, and Kaopectate are useful. **Sucralfate** is a cytoprotective agent that is available for the management of gastrointestinal ulceration. It is a non-absorbable aluminium salt of sucrose octasulfate, when used as a rinse, is only 3% to 5% systemically absorbed. It adheres to ulcer bases, thus creating a surface barrier in the gastrointestinal tract. It has some antibacterial activity and also binds epidermal growth factor and thus might accelerate healing[7].

Nutritional Support: Nutritional intake can be severely compromised by the pain associated with severe oral mucositis. In addition, taste changes can also occur secondary to chemotherapy and/or radiation therapy. There are some diet modifications to be followed are:

Diet that is Acceptable: Liquids, Purees, Ice, Non-acidic fruits, Custards, Soft cheeses, Eggs

Things to Avoid: Rough food (potato chips, toasts), Spices, salt, Acidic fruits

Habits to Avoid: Smoking, Alcohol

Oral Decontamination: It may result in significant positive results in oral mucositis patients. Microbial colonization of oral mucositis lesions exacerbates the severity of oral mucositis. Maintenance of good oral hygiene, brushing with a soft toothbrush and flossing can reduce the severity of oral mucositis. The use of non-medicated rinses, alcohol free rinses (eg, saline or sodium bicarbonate rinses), and the use of a non-absorbable antimicrobial lozenge that combines polymixin, tobramycin, and amphotericin B in conjunction with radiation therapy for head and neck cancer have shown the medication to reduce gram-negative bacterial colonization and to prevent oral ulcers.

Palliation of Dry Mouth: Patients undergoing cancer therapy often develop transient or permanent xerostomia (subjective symptom of dryness) and hyposalivation (objective reduction in salivary flow). Sipping water as needed to alleviate mouth dryness (artificial saliva substitutes like Oralube, Caphosoll and Oasis) are helpful. Rinsing with a solution of half a teaspoon of baking soda half in 1 cup warm water several times a day cleans and lubricates the oral tissues in addition to buffering the oral environment. Chewing sugarless candies and administration of cholinergic agents stimulates the salivary flow.

Therapeutic Interventions: Good oral hygiene, Midline Radiation Blocks, 3-D Radiation Treatment or Intensity Modulated Radiation Therapy (IMRT)**,** Cryotherapy are recommended treatment options in preventing oral mucositis[4].

Cryotherapy: Topical administration of ice chips to the oral cavity during administration of chemotherapy results in decreased delivery of the chemotherapeutic agent to the oral mucosa. This effect is presumably mediated through local vasoconstriction and reduced blood flow. The use of Cryotherapy to reduce oral mucositis in patients receiving bolus doses of 5-fluorouracil, melphalan, and edatrexate. Ice chips are placed in the mouth, beginning 5 minutes before administration of chemotherapy and replenished as needed for up to 30 minutes. It does not have a role in radiation-induced oral mucositis.

ANTI-INFLAMMATORY AGENTS

Benzydamine Hydrochloride: It is a non-steroidal agent that possesses analgesic, anti-inflammatory properties and is mildly anaesthetic. Benzydamine may stabilize cell membranes, inhibit the degranulation of leukocytes, affect cytokine production, and alter the synthesis of prostaglandins. It can be used in the patients administered with the cumulative doses up to 50-Gy radiation therapy.

Saforis: It is a proprietary oral suspension of L-glutamine that enhances the uptake of this amino acid into epithelial cells. Glutamine may reduce mucosal injury by reducing the production of pro-inflammatory cytokines and cytokine-related apoptosis and may promote healing by increasing fibroblast and collagen synthesis.

ANTI-OXIDANTS

Amifostine (Ethylol): It is a sulfhydryl compound that acts by scavenging free radicals generated in tissues exposed to radiation and that promotes repair of damaged DNA. There is reduced uptake of amifostine into tumour, and tumour protection is not seen. Amifostine has been approved in the United States for reduction of renal toxicity secondary to cisplatin administration and for reduction of xerostomia in patients who are treated with radiotherapy.

RK-0202: It consists of the antioxidant N-acetylcysteine in a proprietary matrix for topical application in the oral cavity. Significantly reduces the incidence of severe oral mucositis up to doses of 50-Gy radiation therapy[6].

RECENT ADVANCES FOR THE MANAGEMENT OF THE ORAL MUCOSITIS

Growth Factors: Keratinocyte growth factor (KGF), a member of the fibroblast growth factor family, binds to KGF receptor, accelerating the healing of wounds. Palifermin –is a recombinant human keratinocyte growth factor-1 given intravenous (IV) at a dose of 60 µg/kg per day for 3 days prior to conditioning treatment and for 3 days post transplantation to prevent incidence of WHO grades 3 and 4 oral mucositis.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) given subcutaneously from days 5 to 14 of chemotherapy might reduce the severity and duration of mucositis induced by a number of chemotherapeutic agents including 5-FU, cisplatinum, cyclophosphamide, doxorubicin, etoposide, methotrexate, vinblastine, and Adriamycin.

Low-Level Laser Therapy: Low-energy helium-neon laser is used. It has been speculated that low-level laser therapy may reduce the levels of reactive oxygen species and/or pro-inflammatory cytokines that contribute to the pathogenesis of mucositis[8].

CONCLUSIONS

Oral mucositis affects the quality of life of the patients and their family. The present day management is mostly palliative and supportive care. The role of safe radiotherapy remains the ultimate goal in reducing the symptoms of oral mucositis. Future research is needed for the development of newer drugs in the field of radiation induced oral mucositis.

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